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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/553,656

10/14/2005

Ana Isabel Sanz Molinero

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EXAMINER

KUMAR, VINOD

ART UNIT

PAPER NUMBER

1638

MAIL DATE

DELIVERY MODE

06/20/2008

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/553,656	<b>Applicant(s)</b> SANZ MOLINERO, ANA ISABEL	
	<b>Examiner</b> VINOD KUMAR	<b>Art Unit</b> 1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 08 April 2008.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-7,9,10 and 25-34 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,7,9,10 and 25-34 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 08 April 2008 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                       | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>4/8/08</u> .  | 6) <input type="checkbox"/> Other: _____                          |

***DETAILED ACTION***

***Status of objections and rejections***

1. Amendment filed in the paper of April 8, 2008 is entered.

2. Claims 1-7, 9-10 and newly added claims 25-34 are pending.

Newly added claims 25-34 fall within the scope of elected invention, and is thus included in the present examination.

Claims 8 and 11-24 are cancelled.

Accordingly, claims 1-7, 9-10 and newly added claims 25-34 are examined on merits in this Office action.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. All previous objections to specification and drawings have been withdrawn in light of amendments to the specification and drawings filed in the paper of April 8, 2008.

5. Rejection of claims 1-5 and 9-10 under 35 USC 102(b) is withdrawn in light of claim amendment filed in the paper of April 8, 2008.

***Claim Objections***

6. Claims 1, 3 and 9 are objected to because of the following informalities:

Claim 1 is objected for having improper article "a" before "nucleic acid" in line 4. It is suggested to change "a" to --the--.

Claim 3 is objected for lacking punctuation mark at the end of claim.

Claim 9 is objected for reciting "1 or 5 to 7" which does not read properly. It is suggested to change "1 or 5 to 7" to --1, 5, 6 or 7--.

These claim objections have been necessitated due to claim amendment filed in the paper of April 8, 2008.

***Claim Rejections - 35 USC § 112***

7. Claims 1-7, 9-10 and newly added claims 25-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite in their recitations “genetic modification” because there is insufficient antecedent basis for this limitation in the claim.

Dependent claims are also rejected because they fail to overcome the deficiency of parent claims 1 or 25.

This rejection has been necessitated due to the claim amendment filed in the paper of April 8, 2008.

***Claim Rejections - 35 USC § 112***

8. Claims 1-7, 9-10 remain, and newly added claims 25-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of increasing plant seed yield comprising transformation of a plant with a nucleic acid sequence encoding a metallothionein protein as defined in SEQ ID NO: 2, does not reasonably provide enablement for (a) a nucleic acid sequence encoding any metallothionein protein or encoding any type 2 metallothionein protein, (b) a nucleic acid sequence encoding a metallothionein protein having 95% identity to SEQ ID NO: 2, and

(c) increasing expression of a nucleic acid encoding a metallothionein protein in a plant by a method other than transforming said plant with said nucleic acid. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for the reasons of record stated in the Office action mailed on October 18, 2007. Applicant traverses the rejection in the paper filed on April 8, 2008.

Applicant argues that metallothioneins are well known in art, and the information available for animal and fungal metallothioneins of type 2 can be extrapolated to plant type 2 metallothioneins. Applicant further argues that document cited on page 10 of the Office action does not relate to metallothioneins and cannot be extrapolated as such to metallothionein proteins. Applicant further argues that that comments on page 11 of the Office action is directed to the function of metallothioneins under natural conditions, and thus cannot be compared to the function of metallothioneins expressed under artificial conditions (response, page 15, last paragraph through the paragraph bridging pages 15 and 16).

Applicant's arguments are fully considered but are deemed to be unpersuasive.

Newly added claim 25 is directed to any metallothionein protein and newly added claim 30 is directed to any type 2 metallothionein protein that have the property of increasing yield upon expression in a plant.

It is maintained that while the specification teaches a nucleotide sequences encoding SEQ ID NO: 2, it does not teach full scope of nucleotide sequences encoding other metallothionein protein that confer yield enhancement.

It is maintained that the state of art teach that the precise function of metallothioneins remains to be elucidated. See for example, Robinson et al. (Biochem. J., 295:1-10, 1993; see in particular, page 1, left column, lines 8-30; page 5, table 1; page 8, last paragraph in right column through the end of 1<sup>st</sup> paragraph of page 9) who suggest that factors (stress and non-stress related) responsible for the induction of metallothionein gene expression vary significantly in the cells of different organisms, including plants, implying that members of metallothionein gene family are implicated in diverse cellular functions within the plant cell. Also see Chang et al. (Planta, 218:449-455, 2004; see in particular, abstract, page 449, right column; page 450, left column above materials and methods; page 452, figures 4-5; page 453, figures 6-7), who clearly suggest that class-2 metallothionein from sunflower might be involved in transport and availability of  $\text{Cu}^{2+}$  and  $\text{Zn}^{2+}$  to some apometal enzymes or apo-metal proteins.

Teachings of Robinson et al. or Chang et al. clearly suggest that not all metallothionein or type 2 metallothioneins would be expected to have similar biological role in a plant cell. Thus, it is maintained that one of skilled in the art would not expect all metallothioneins including class-2 metallothioneins to cause yield and/or growth enhancement to plants upon overexpression in a transgenic plant. The specification does not teach which metallothioneins or class-2 metallothioneins would confer this trait and which would not.

While the specification teaches a nucleotide sequences encoding SEQ ID NO: 2, it does not enable all nucleotide sequences encoding other metallothioneins or type 2 metallothioneins. Undue experimentation by one skilled in art is required to isolate

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other metallothioneins or type 2 metallothioneins from other sources. See In re Bell, 26 USPQ2d 1529, 1532 (Fed. Cir. 1993) and In re Deuel, 34 USPQ2d, 1210 (Fed. Cir. 1995), which teach that the mere existence of a protein does not enable claims drawn to a nucleic acid encoding that protein. See also Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016 at page 1027, where it is taught that the disclosure of a few gene sequences did not enable claims broadly drawn to any analog thereof.

In the absence of guidance, undue experimentation would have been required by one skilled artisan at the time the claimed invention was made to isolate other metallothioneins or class-2 metallothioneins from other sources and use them in a method of obtaining plant with increased growth/and or yield.

Claim 2 and newly added claim 32 is directed to a nucleotide sequence encoding a polypeptide having 95% identity to instant SEQ ID NO: 2.

The instant specification fails to provide guidance on how to make nucleic acid sequences encoding a polypeptide having 95% sequence identity to SEQ ID NO: 2, and retaining the function of increasing plant yield upon expression of said nucleic acid sequence in a plant.

Nucleic acid sequences having 95% sequence identity to the 81 amino acid long SEQ ID NO: 2 would encode proteins with 4 amino acid substitutions relative to SEQ ID NO: 2.

Making all possible single amino acid substitutions in an 81 amino acid long protein like that encoded by SEQ ID NO: 1 would require making and analyzing  $19^{81}$  nucleic acid sequences; these proteins would have 98.7% identity to SEQ ID NO: 2.

Because nucleic acid sequences encoding proteins with 95% sequence identity

to the 81 amino acid long SEQ ID NO: 2 which would encode proteins with 4 amino acid substitutions relative to SEQ ID NO: 2, many more than  $19^{81}$  nucleic acid sequences would need to be made and analyzed.

It is maintained that the instant specification fails to provide guidance for which amino acids of SEQ ID NO: 2 can be altered and to which other amino acids, and which amino acids must not be changed, to maintain biological activity of the encoded protein. The specification also fails to provide guidance for which amino acids can be deleted and which regions of the protein can tolerate insertions and still produce a functional enzyme.

It is further maintained that making amino acid changes in SEQ ID NO: 2 protein is unpredictable. While it is known that many amino acid substitutions, additions or deletions are generally possible in any given protein the positions within the protein's sequence where such amino acid changes can be made with a reasonable expectation of success (without altering protein function) are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see for example, Wells, *Biochemistry* 29:8509-8517, 1990, see pages 8511-8512, tables 1-2; Ngo et al., *The Protein Folding Problem and Tertiary Structure Prediction*, K. Merz., and S. Le Grand (eds.) pp. 492-495, 1994; see page 491, 1<sup>st</sup> paragraph).



It is thus maintained that making and analyzing proteins with unspecified changes in the amino acid sequence of SEQ ID NO: 2 that also have the biological activity of increasing seed yield would require undue experimentation.

It is further maintained that the instant specification fails to provide guidance on a method of increasing seed yield comprising increasing expression of a nucleic acid sequence encoding metallothionein protein (SEQ ID NO: 2) in any manner other than transforming a plant with a nucleic acid sequence encoding SEQ ID NO: 2. The specification does not provide guidance on co-factors, or positive regulators of metallothionein, for example that makes the metallothionein gene to overexpress to produce a plant with said characteristics. The specification provides no guidance on upstream regulatory factors, for example, that may be necessary in stimulating the overexpression endogenous metallothionein. In the absence guidance, it is maintained that undue experimentation would have been required by a skilled artisan at the time the claimed invention was made to determine how a plant with increased seed yield could have been produced by a method that comprises increasing the expression of a nucleic acid sequence encoding a metallothionein protein (SEQ ID NO: 2) without transforming the plant with a nucleic acid sequence encoding a metallothionein protein (SEQ ID NO: 2). It is noted that Applicant has not addressed this issue of scope of enablement in their response of April 8, 2008.

Given the breadth of the claims, unpredictability of the art and lack of guidance of the specification, as discussed above, undue experimentation would be required by one skilled in the art to make and use the claimed invention. Therefore, it is maintained that

the claimed invention is not enabled as commensurate in scope with the claims.

9. Claims 1-7, 9-10 remain and newly added claims 25-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons of record stated in the Office action mailed on October 18, 2007.

It is noted Applicant did not provided any arguments in their traversal. It is also noted that new limitation comprising a 95% identity to SEQ ID NO: 2 also fails to meet written description requirements for the same reasons of record. Accordingly, the rejection is maintained.

### ***Claim Rejections - 35 USC § 102***

10. Newly added claims 25-31, and 33-34 are rejected under 35 U.S.C. 102(b) as being anticipated by Basel et al. (WIPO Publication No. WO 98/36084, Published 20 August, 1998, Applicant's IDS) for the reasons of record as previously applied to claims 1-5 and 8-10 in the Office action mailed on October 18, 2007. Applicant traverses the rejection in the paper filed April 8, 2008.

Applicant argues that there is no established link between faster growth rates and increase in yield. Applicant cites unrelated art of He et al. and Jeon et al. to support their arguments (response, page 18, 7-16).

Applicant's arguments are fully considered but are deemed to be unpersuasive.

It is important to note that teachings of He et al. or Jeon et al. are not directed to metallothionein proteins. Thus, it is improper to argue against the inherency by citing unrelated proteins.

It is thus maintained that Basel et al. disclose a method of making a transgenic plant with increased growth and development comprising introducing and overexpressing a nucleic acid sequence encoding a metallothionein, and wherein the nucleic acid is expressed under a constitutive promoter. See in particular, pages 2, lines 11-23; page 9, lines 7-14; page 35, line 6; page 37, line 12; SEQ ID NO: 7.

The properties of increased seed yield and/or increased biomass would be inherent to the method of increasing growth and development disclosed in the reference which comprises overexpression of said metallothionein protein in the transgenic plant.

If the body of a claim fully and intrinsically sets forth all of the limitations of the claimed invention, rather than any distinct definition of any of the claimed invention's limitations, then preamble is not considered a limitation and is of no significance to claim construction. See MPEP 2111.02.

Also see *In re Cruciferous Sprout Litig.*, 301 F.3d 1343,1346-48, 64 USPQ2d 1202, 1204-05 (Fed. Cir. 2002) where a claim at issue was directed to a method of preparing a food rich in glucosinolates wherein cruciferous sprouts are harvested prior to the 2-leaf stage. The court held that the preamble phrase "rich in glucosinolates" helps define the claimed invention, as evidenced by the specification and prosecution history, and thus is a limitation of the claim (although the claim was anticipated by prior art that produced sprouts inherently "rich in glucosinolates").

Also see *Integra LifeSciences I Ltd. V. Merck KGaA* 50 USPQ2d 1846, 1850 (DC Scalif 1999), which teaches that where the prior art teaches all of the required steps to practice the claimed method and no additional manipulation is required to produce the claimed result, then prior art anticipates the claimed invention.

Accordingly, Basel et al. anticipated the claimed invention.

### ***Claim Rejections - 35 USC § 103***

11. Claims 1-7, 9-10 remain, and newly added claims 25-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Basel et al. (WIPO Publication No. WO 98/36084, Published 20 August, 1998, Applicant's IDS) in view of Zhou et al. (Mol. Gen. Genet. 248:318-328, 1995) for the reasons of record as stated in the Office action mailed on October 18, 2007. Applicant traverses the rejection in the paper filed April 8, 2008.

Applicant while admitting that Basel et al. teach a method of making a transgenic plant, argues that the reference does not teach a method of making plant with increased growth and development. Applicant further argues that neither Zhou et al. or Basel et al. suggest that ectopically expressing in a plant a metallothionein gene would result in increased yield. Applicant further argues that the expression pattern of MT2 taught in Zhou et al. does not provide any suggestion as to the effect of MT2 on plant yield, for example, expression in the inflorescence may affect development of flowers but is not predictive for the development of seeds (response, page 19, lines 1-14).

Applicant's arguments are fully considered but are deemed to be unpersuasive.

It is maintained that Basel et al. teach a method of making a transgenic plant with increased growth and development comprising introducing and overexpressing a nucleic acid sequence encoding a metallothionein, and wherein the nucleic acid is expressed under a constitutive promoter. See in particular, pages 2, lines 11-23; page 9, lines 7-14; page 35, line 6; page 37, line 12; SEQ ID NO: 7.

It is also maintained that Zhou et al. teach a nucleic acid sequence encoding *Arabidopsis* type 2 metallothionein protein (MT2a) which has 100% sequence identity to instant SEQ ID NO: 2. The reference further teaches that nucleic acid sequences encoding members of metallothionein proteins are differentially regulated. In particular, MT2a is overexpressed in the mature leaves and inflorescence, compared to other members of the gene family. See in particular, page 318, abstract; page 322, figure 3; page 324, figures 6 and 7; page 326, 2<sup>nd</sup> column through the end of 1<sup>st</sup> column of page 327.

It is therefore, maintained that it would have been prima facie obvious to one of ordinary skill in the art to modify the method of making a transgenic plant with increased growth and development as taught by Basel et al., to substitute the coding sequence encoding Basel et al. metallothionein protein with a nucleotide sequence encoding Zhou et al. type 2 metallothionein protein to obtain a transgenic plant and transgenic seed expressing Zhou et al. metallothionein protein.

Given that Basel et al. teach that overexpressing a metallothionein protein in a plant improves growth and development and Zhou et al. teach that type 2 metallothionein proteins (MT2a, in particular) are highly expressed in tissues like leaf and inflorescence, it would have been obvious and within the scope of an ordinary skill

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in the art to have been motivated to express Zhou et al. sequence in a plant to obtain transgenic plants having improved growth and development with a reasonable expectation of success. It would have been obvious that increased growth and development would have improved yield, such as seed yield with a reasonable expectation of success.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, it would have been obvious and within the scope of an ordinary skill in the art to combine the teachings of Basel et al. and Zhou et al. to arrive at the claimed invention with a reasonable expectation of success.

Thus, it is maintained that the claimed invention as a whole is prima facie obvious over the combined teachings of the prior art.

### ***Conclusions***

12. Claims 1-7, 9-10 remain and newly added claims 25-34 are rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

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§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

***Contact Information***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vinod Kumar whose telephone number is (571) 272-4445. The examiner can normally be reached on 8.30 a.m. to 5.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg can be reached on (571) 272-0975. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Phuong T. Bui/

Primary Examiner, Art Unit 1638